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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,545	ZLOKOVIC ET AL.	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14-22 and 27-49* is/are pending in the application.

4a) Of the above claim(s) *27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14-22 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 18 March 2009 and the sequence listing filed 29 April 2009 have been entered. Claims 12, 14 - 22, and 27 - 49 are pending.

Election/Restrictions

2. At p. 8 first paragraph of the remarks filed 18 March 2009, applicant requested rejoinder of claims 21 - 22 and 27 - 28 as the claims have been re-written and are now drawn to the elected invention. This argument is persuasive to the extent it applies to claims 21 - 22. Claims 21 - 22, as newly amended, are drawn to methods of administering activated protein C, at least one prodrug, or at last one functional variant thereof. These claims are not patentably distinct from the other claims under examination, and therefore claims 21 - 22 are rejoined. However, claims 27 - 28 are drawn to methods of using different products, namely PAR-1 or PAR-3 or EPCR agonists. These are not the same as protein C, and therefore are patentably distinct. The restriction between the claims under examination and present claims 27 - 28 is maintained.

3. Claims 27 - 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 14 July 2008.

4. This application contains claims 27 - 28 drawn to an invention nonelected with traverse in the reply filed on 14 July 2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

5. Claims 12, 14 - 22, and 29 - 49 are under examination.

Withdrawn Rejections and Objections

6. The following rejections and objections set forth in the previous office action are withdrawn:

A. The rejections under 35 USC 112, second paragraph, are withdrawn in light of the amendments and arguments. Note however the new rejection under 35 USC 112, second paragraph, drawn to a substantially different issue.

B. The rejection under 35 USC 112, first paragraph, is withdrawn in light of the amendments. Note however the rejection of newly-amended and rejoined claims 21-22, and new claims 33 - 36, 38 - 46, and 48 - 49 under 35 USC 112, first paragraph.

C. The rejections under 35 USC 102 are withdrawn in light of the amendments. Applicant has incorporated the limitations of claim 20, which was not subject to these rejections, into independent claim 12.

D. The rejection under 35 USC 103(a) is withdrawn in light of the amendments. The reference by Kureshi does not cure the deficiencies of Griffin with respect to the specific mutations recited in claim 12.

E. The provisional obviousness-type double-patenting rejection over copending application 10/886766 is moot. The application is no longer pending; since the last office action was mailed the application has issued as U.S. Patent 7,498,305. Note however the obviousness-type double-patenting rejection over this patent.

F. The obviousness-type double patent rejections of U.S. Patents 5,084,274 and 7,074,402, and over copending application 11/632850 are withdrawn in light of the amendments to claim 12. Claim 12 has been amended to incorporate the limitations of previous claim 20, which was not included in these rejections. Note however obviousness-type double-patenting rejections of newly-amended and newly-presented claims over those same patents and applications set forth in this office action.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 14 - 20, 29 - 32, 37-38, and 47 - 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 20, 37, and 47 each recite mutations in specific amino acid residue numbers of protein C, and refer to the amino acid sequence in U.S. Patent 4,775,624. The mutations are to be selected from the group consisting of KKK191-193AAA and RR229/230AA. The claims are confusing because the amino acid sequence from protein C, which appears at columns 5 - 8 of the '624 patent, does not have LYS (K) amino acids at residues 191-193 and does not have

ARG (R) amino acids at residues 229 - 230. Thus it is unclear which mutations are encompassed by the claims.

Additionally, these claims are indefinite because it is unclear how many amino acid residues must be changed. For example, in claim 12, must all three amino acid residues (i.e., each of 191 - 193) be changed from K to A? Would a method of administering activated protein C with a K→A mutation at residue 191 only infringe upon this claim? If the mutant further comprised a single R→A mutation at either residue 229 or 230, but not both, would claim 20 be infringed? It is unclear whether all the recited amino acid residues need to be changed, or whether changing any one of the recited residues is sufficient. Since the claims recite "at least one mutation" (see for example claim 12), the claims imply that changing one amino acid alone is sufficient. However, since the claims also recite multiple changed amino acids, this implies that multiple amino acids must be changed.

Claims 38 and 48 are confusing because they encompass administration of activated protein C, since they depend from claims which allow for administration of wild-type activated protein C, which is known to be an anti-coagulant, but state that "the effective amount results in at least reduced or insignificant anticoagulation". It is unclear how a known anticoagulant could lead reduced or insignificant anticoagulation. Furthermore, it is unclear what "reduced" means, since it is not being compared to anything. Does it refer to a measure of coagulation (for example, prothrombin time) in the same subject prior to administration of the compound? Does it refer to a reduction in anticoagulation in a control population? If so, what is the relevant control? Is it a population of unaffected persons? Is it a population of persons with the relevant disease, but who have not been administered activated protein C?

Claim 49 is also confusing. It recites "the at most 0.02 milligrams", implying that the dose administered is 0.02 mg over 72 hours or less. However, this claim refers back to claim 40, which is drawn to administration of 0.02 mg per kg of body weight. It is unclear whether claim 49 is drawn to administering 0.02 mg/kg, which would be 1.4 mg for a 70 kg person, or 0.02 mg total.

The remaining claims (i.e., claims 14 - 19, 29 - 32) each depend from rejected claim 12 but do not clarify the scope of patent protection sought and therefore remain rejected as well.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21 - 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 21 and dependent claim 22 each are drawn to methods of using variants of activated protein C (APC) as well as prodrugs. As set forth in the previous office action, the full genus of variants and prodrugs has not been described by the specification. First, it is noted that claim 21 as written is very broad in that it is not limited to administration of prodrugs of activated protein C, but rather lists "...an effective amount of activated protein C, at least one prodrug, or at least one functional variant thereof". That is, the claim is drawn to administration of either any prodrug or variant thereof, or in the alternative to activated protein C. While the specification very generally contemplates administration of prodrugs and variants of APC (see for example p. 6 line 28, p. 12 lines 24 - 26 which refers to certain specific mutants of APC that retain anticoagulant activity, as well as p. 15 first complete paragraph), the specification fails to disclose the structures that are common to all members of the genus of proteins to be administered. Factors to be considered when determining compliance with the written description requirement include, but are not limited to, disclosure of complete or partial structure, chemical formulae, diagrams, or functional recitations when coupled with a known or disclosed structure-function correlation. See for example the Written Description Training Materials, available on USPTO's website at http://www.uspto.gov/web/menu/written.pdf , particularly p. 1 which describes the criteria. In this case, since the specification fails to disclose the structures common to all prodrugs, whether or not they are prodrugs of activated protein C, and all variants of either activated protein C, prodrugs of same, or prodrugs of some other product, the written description requirement has not been satisfied.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21 - 22 are rejected under 35 U.S.C. 102(b) as being anticpated by Griffin (WO 01/56532, published 9 August 2001, of record).

Griffin teaches administration of activated protein C (APC), as recited in independent claim 21. This is the sole step of claim 21. While the reference is silent as to whether or not p53 signaling is reduced, since Griffin teaches all relevant starting materials (activated protein C) and steps (administering to a subject, the reference anticipates this claim. Similarly, claim 22 is anticipated as it recites an effect which will necessarily happen following administration.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 40 - 41, 43 - 46, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffin (WO 01/56532).

Griffin teaches treating stroke, as recited in claim 43, and neurodegenerative diseases, as recited inc claims 44 - 45, by administering activated protein C. See for example p. 13 lines 1 - 5 and p. 15 lines 20 - 29. Griffin teaches that the dose administered should be about 0.01 mg/kg/hour (see for example p. 21 lines 14 - 16). The dose can be administered for as little as four hours (p. 21 lines 16 - 19), which leads to a total dose of 0.04 mg/kg. However, Griffin does not explicitly teach administering a maximum of 0.02 mg/kg, as recited in claim 40.

Nevertheless, it would have been obvious to one of ordinary skill in the art to modify the method of Griffin by adjusting the dose of activated protein C. Griffin teaches that when other compounds, such as Protein S, is coadministered, the amount of activated protein C can be reduced (p. 22 lines 4 - 5). Therefore one of ordinary skill in the art would find it obvious to modify the dose from that disclosed by Griffin.

Claim 41 is included in this rejection as the cells damaged and stressed by stroke are in the brain. Claim 46 is included as the property must necessarily be present, since claim 46 allows for administration of activated hPC as taught by Griffin. Note that Griffin teaches that activated protein C acts as an anti-inflammatory (p. 16 paragraphs 2, 4, and 5). Claim 49 is confusing as described in the rejection under 35 USC 112, second paragraph above but nonetheless is included in this rejection. Since it would have been obvious to administer the dose recited in parent claim 40, and Griffin indicates that the dose can be given for four hours, claim 49 is obvious as well.

11. Claims 33 - 36, 39 - 46, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffin as applied to claims 40 - 41, 43 - 46, and 49 above, and further in view of Glantz 1994 (Neurology 44:2020-2027).

The reasons why claims 40 - 41, 43 - 46, and 49 are obvious over Griffin are set forth in the rejection above. Griffin teaches treating brain cells for injury, including that caused by ischemia, as well as treating Alzheimer's disease, by administering activated protein C, recited in independent claims 33 and 40. Griffin explicitly teaches 0.04 mg/kg as encompassed by claims 33 - 34, and gives guidance to reducing the dose down to 0.02 mg/kg as recited in claims 35 and 40. Griffin teaches that activated protein C is known to act as an anticoagulant as well as an anti-inflammatory (see for example p. 1 lines 9 - 30). However Griffin does not explicitly teach treating brain radiation injury as recited in claims 33 and 42.

Glantz teaches treating brain injury induced by radiation by administering anticoagulants. The reference teaches that both warfarin and heparin were effective in ameliorating radiation-induced damage (see paragraph beginning at end of p. 2023). This is on point to claims 33 and 42, each drawn to treating radiation-induced injury in the brain. However Glantz does not teach administering activated protein C, required by both independent claims 33 and 40.

Nevertheless, it would have been obvious to one of ordinary skill in the art to administer activated protein C for treating radiation injury in the brain, with a reasonable expectation of

success. It is *prima facie* obvious to substitute known equivalents for one another (MPEP § 2144.06(II)), and Griffin teaches activated protein C acts as an anti-coagulant, which is what Glantz teaches is effective in treating this type of injury. Therefore substituting the activated protein C of Griffin for the warfarin or heparin of Glantz would have been obvious.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 21-22, 40 - 41, 43, 46, and 49 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 - 7 of U.S. Patent No. 7,074,402. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims encompass administration of activated protein C to patients having or at risk of having stroke. Applicant argued, in the paragraph spanning pp. 11 - 12 of the remarks filed 18 March 2009, that the ownership is not identical and therefore the

rejection should be withdrawn. Applicant's argument has been fully considered but is not persuasive. Since there is a common assignee (Scripps) and identical inventors (both Zlokovic and Griffin are the only named inventors in each case), maintaining the rejection is proper. See MPEP § 804, in particular Chart II-B.

14. Claims 21-22, 40 - 41, 43, 46, and 49 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 5,084,274. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims encompass administration of activated protein C to patients with ischemia as recited in instant claim 43. Note the ischemia recited in claim 43 is not limited to cerebral ischemia. Furthermore claim 21 is drawn to administration to any patient.

Applicant argued, on p. 12 of the remarks filed 18 March 2009, that the ownership is not identical and therefore the rejection should be withdrawn. Applicant's argument has been fully considered but is not persuasive. Since there is a common assignee (Scripps) and a common inventor (Griffin), maintaining the rejection is proper. See MPEP § 804, in particular Chart II-B.

15. Claims 12, 14 - 22, 29 - 49 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 12 and 42 - 49 of copending Application No. 11/589371. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims encompass administration of the specific mutants recited in instant claims 12, 37, and 47 for treatment of the same diseases and conditions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant argued, on p. 12 of the remarks filed 18 March 2009, that the ownership is not identical and therefore the rejection should be withdrawn. Applicant's argument has been fully considered but is not persuasive. Since there is a common assignee (Scripps) and a common inventor (Griffin), maintaining the rejection is proper. See MPEP § 804, in particular Chart I-B.

16. Claims 21-22, 40 - 41, 43, 46, and 48 - 49 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 - 16 of copending Application No. 11/632580. Although the conflicting claims are not identical, they are

not patentably distinct from each other because in each case the claims encompass administration of activated protein C to patients who have had a stroke.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

A provisional rejection over the '850 application was made in the previous office action. Applicant argues, on p. 12 of the remarks, that the rejection should be withdrawn as that application is assigned to University of Rochester, whereas the present application is assigned to University of Rochester, Scripps Research Institute and Socratech LLC. Although the applications are not identically assigned, there is at least one common inventor (Zlokovic) and one common assignee (Rochester). According to MPEP § 804, in particular Chart I-B, double-patenting rejections are proper in this situation.

17. Claims 12, 14 - 22, 29 - 49 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 - 21 of U.S. Patent No. 7,498,305. Although the conflicting claims are not identical, they are not patentably distinct from each other because the encompass administration of the specific mutants recited in instant claims 12, 37, and 47 for treatment of the same diseases and conditions.

In the last office action, a rejection was made over copending application 10/886766. That application has now issued as the '305 patent. Applicant argued that the rejection over the copending '766 application should be withdrawn as assignees are not identical between that case and the present case. Applicant's argument has been fully considered but is not persuasive. Since there is a common assignee (Scripps) and a common inventor (Griffin), maintaining the rejection is proper. See MPEP § 804, in particular Chart II-B.

Conclusion

18. No claim is allowed.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
July 1, 2009